DOCKET NO.: DITE-099

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT:	William McBride, et al.		
SERIAL NO.:	08/253,973	EXAMINER:	M. Hartley
FILING DATE:	June 3, 1994	GROUP:	1616

TITLE: **MONOAMINE, DIAMIDE, THIOL-CONTAINING METAL CHELATING AGENTS**

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Patricia A. McDaniels
Patricia A. McDaniels
Date: September 7, 1999

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

APPEAL BRIEF

This Brief is submitted, in triplicate, in response to the Advisory Action dated August 18, 1999, maintaining the Examiner's final rejection of claims 2 through 8 and 10.

Authorization is hereby given to charge the fee of $150.00, and any other fee which may be due with regard to this submission, or to credit any overpayment, to Deposit Account No. 50-0452.

I. REAL PARTY IN INTEREST

The real party in interest is Diatide, Inc., a Delaware corporation having its principal place of business at 9 Delta Drive, Londonderry, New Hampshire. The inventors' assignment of the instant application to Diatech, Inc. is recorded in the Assignment Branch of the Patent and Trademark Office at Reel 7072, Frame 0396, and the Certificate of Corporate Name Change from Diatech, Inc. to Diatide, Inc. is recorded against the instant application at Reel 9453, Frame 0097.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pending at this time. Appellants have brought two patents to the Examiner's attention, U.S.Pat.Nos. 5,662,885 and 5,780,006, which claim potentially interfering subject matter. By virtue of their earlier filing date and priority claims, Appellants would be senior party in an interference between the instant application and U.S.Pat.Nos. 5,662,885 and 5,780,006.

III. STATUS OF CLAIMS

The application as filed contained 36 claims. Claim 37 was added in the amendment filed December 15, 1997.

cancelled claims: 1, 9, and 11-37

rejected claims: 2-8 and 10

claims on appeal: 2-8 and 10.

IV. STATUS OF AMENDMENTS

The amendment after final filed on June 24, 1999 has been entered.

V. SUMMARY OF INVENTION

The invention is a reagent comprising a targeting moiety covalently linked to a monoamine, diamide, single thiol metal chelator of a particular formula (page 10, lines 11-25; page 12, line 3 to page 15, line 20). The reagents of the invention are combined with metal ions to make radiopharmaceuticals which localize at specific target sites in a mammalian body and which are used for diagnosis and therapy of diseases (page 10, lines 2-10; page 19, lines 1-4; page 20, lines 17-28; page 21, lines 2-7 and lines 24-30; page 28, lines 18-26; page 29, lines 13-15; Examples 2 through 8).

VI. ISSUES

A. Can the Examiner ignore express limitations in a reference when rejecting claims under 35 U.S.C. § 103?

B. Is a rejection under 35 U.S.C. § 103 proper when the primary reference does not direct those of skill to the claimed invention?

C. Is a rejection under 35 U.S.C. § 103 based on a combination of references proper when neither reference contains any teaching or suggestion to make the combination?

D. Is a rejection under 35 U.S.C. § 103 proper when the suggested combination is inoperative?

E. Is the Examiner's admitted use of hindsight reconstruction proper on the present facts?

F. Does the suggested combination of references in fact yield the presently claimed invention?

VII. GROUPING OF CLAIMS

The claims do not stand or fall together. Appellants note that each of the chelators of claims 3 through 7 is a separate and distinct species of the generic formula of claim 2, and for that reason claims 3 through 7 do not stand or fall together. Each of the chelators of claims 3 through 7 is patentable over each of the other chelators, since each chelator is structurally distinct from each other chelator. The chelators of claims 7, 8 and 10 stand or fall together.

VIII. ARGUMENT

Claims 2-8 and 10 stand rejected as being unpatentable under § 103 over U.S.Pat.No. 5,688,485 (Harris) in view of U.S.Pat.No. 5,091,514 (Fritzberg '514). The rejection is based on the following premises:

- Harris discloses SNNN or NNNS ligands within the scope of the present claims, because one of skill would have recognized that Harris teaches all ligands within the scope of the disclosed formula;

- one of skill would have been motivated to further improve the biodistribution of the ligands of Harris by conjugating a targeting agent thereto as shown by Fritzberg;

- *In re McLaughlin*, 170 USPQ 209 (CCPA 1971) justifies hindsight reconstruction in the present case.

A. The Examiner cannot ignore limitations which are expressly stated in a reference.

At page 2 of the Office Action of April 9, 1999, the Examiner asserts that:

> [a]lthough the preferred embodiments of the Harris invention may be diamine or diaminedithiol, there are no provisos set forth in the description of the formula which limits the formula to such compounds.

In fact, at col. 3, lines 16-17, with reference to formula I, Harris states:

> [t]o achieve these objectives there is provided an ester-substituted **diaminethiol** of the general formula. . . (*emphasis added*)

and at col. 3, lines 65-67, with reference to formula II, Harris states:

> [f]urther provided is a radiopharmaceutical consisting of a complex of an ester-substituted **diaminethiol** as described above and a radionuclide, having the general formula: . . . (*emphasis added*)

Further, the reference repeatedly describes the compounds as "diaminethiol"[1], "diaminedithiol"[2], or "diamidodithiol"[3].

In the Advisory Action dated August 18, 1999, the Examiner states:

> . . .the compounds disclosed by Harris are not limited to "diaminethiol" compounds as stated by applicant. This is clear from compound XVII (column 8) and compound XIX (column 9) which are not "diaminethiols".

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[1] *See*, col. 3, line 17 and line 66; col. 4, line 48; col. 6, line 5; col. 9, line 42 and line 50; col. 10, line 6, line 15, line 62, and line 67.

[2] *See*, col. 4, line 60, line 61, line 65; col. 5, line 3, line 7, line 47, line 52, line 57; col. 6, line 14, line 16, line 21, and line 63; col. 7, line 37, line 53, line 55; col. 11, line 6, line 35, line 44, line 50; col. 8, line 7 and line 44.

[3] *See*, col. 8, line 31, line 46 and line 66.

Appellants agree that formulae XVII and XIX are not "diaminethiols"; however, the Examiner has again ignored the entirety of the Harris disclosure. At col. 8, line 32, Harris states: "[d]iamidodithiol ligands of formula XVII can be prepared. . ."; and at col. 8, lines 66-67: "[t]he structurally similar diamidodithiol ligands of structure XIX can generally be prepared. . ." Moreover, formulae XVII and XIX clearly depict the presence of two sulfur atoms. Formulae XVII and XIX have no relevance to the monoamine, diamide, single thiol chelator of the present claims.

In the Office Action dated April 9, 1999, the Examiner incorrectly applied *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 10 U.S.P.Q.2d 1843 (Fed.Cir. 1989), *In re Susi*, 169 USPQ 423 (CCPA 1971) and *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed.Cir. 1994). None of these cases is on point with the present facts, since in each of the cited cases, the claimed invention actually fell within the genus disclosed in the prior art. In contrast, the present claims cannot reasonably be construed as falling within any genus disclosed by Harris.

The Examiner has cited *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, to support the proposition that "all disclosures of the prior art, including examples and unpreferred embodiments, must be considered", 10 U.S.P.Q.2d at 1846. The claims in *Merck & Co. Inc. v. Biocraft Laboratories Inc.* were directed to compositions of particular ratios of amiloride hydrochloride and hydrochlorothiazide for use as diuretics. 10 U.S.P.Q.2d at 1845. The prior art disclosed amiloride as a member of the chemical class, the 3-amino-5, 6-disubstituted pyrazinoyl guanidines. *Id.* In addition, the reference disclosed that these substituted guanidines could be used in combination with other classes of diuretic agents, including hydrochlorothiazide, to prevent loss of potassium. *Id.* The Court held that the reference taught a genus encompassing the claims of the challenged patent. *Id.*

In re Susi and *In re Gurley* have been cited to support the proposition that examples and preferred embodiments do not constitute a teaching away from a broader disclosure of nonpreferred embodiments, *In re Susi*, 169 U.S.P.Q. at 426 n.3; *In re Gurley*, 31 U.S.P.Q.2d at 1132. The claims of *In re Susi* were directed to a polymer stabilized by a combination of a substituted phenol with certain benzylidene malonate acid di-esters.

169 U.S.P.Q. at 425. Two primary references were cited, the first of which (Knapp) disclosed stabilization of plastics from ultraviolet light induced degradation by a combination of a nitrophenol or a formylphenol with benzylidene malonate acid di-esters which contained an additional hydroxyl substitution on the benzene ring. *Id.* The second primary reference (Lauerer) disclosed plastic compositions containing ultraviolet light absorbers having a generic formula which encompassed benzylidene malonate acid di-esters. *Id.* Thus in *In re Susi* each primary reference actually disclosed the genus of the claimed invention, in contrast to the present fact pattern.

The claims of *In re Gurley* were directed to an epoxy based printed circuit material for forming circuit boards. The cited reference, Yamagouchi, disclosed printed circuit material comprising a fibrous substrate impregnated with a polyester-imide resin. 31 U.S.P.Q.2d at 1131. Yamagouchi also disclosed that use of epoxy-impregnated fibrous substrate for making circuit boards was known, but that such circuit boards were inferior to those impregnated with polyester-imides. *Id.* As in *In re Susi*, the reference cited in *In re Gurley* actually disclosed the claimed invention.

In contrast to the facts of *Merck & Co. v. Biocraft*, *In re Susi*, and *In re Gurley*, the presently claimed invention is not even a nonpreferred embodiment of any formula disclosed in Harris, when the reference is properly construed. No reasonable chemist would have recognized Harris as teaching all ligands that fall within the scope of formula, because no reasonable chemist would have read Harris' formula without applying Harris' express limitations. The Harris formulae can only reasonably be construed as encompassing diaminethiols, diaminedithiols, and diamidodithiols, because Harris does not describe his chelators as encompassing any other configurations. The Examiner's construction of the Harris formulae to encompass the monoamine, diamide, thiol chelator of the present claims has no basis in logic or sound scientific reasoning, *In re Soli*, 137 U.S.P.Q. 797, 801 (CCPA 1963), and for this reason the rejection should be overruled.

B. The generic disclosure of Harris does not direct those of skill to the presently claimed invention.

In the Advisory Action dated August 18, 1999, the Examiner opines that:

> Since the formula disclosed by Harris encompasses the instantly claimed compounds, one of ordinary skill in the art would have been motivated to prepare such compounds.

As discussed above, none of the Harris formulae would be interpreted by a chemist of ordinary skill to encompass a monoamine, diamide, single thiol chelator. In fact, chemists of skill would construe Harris as teaching away from the presently claimed chelators since all chelators disclosed in Harris are expressly described as diaminethiols, diaminedithiols, or diamidodithiols.

In re Gurley is instructive in that the case defines a "teaching away".

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

31 U.S.P.Q.2d at 1131. Because of the express limitations applied to each formula, Harris leads those of skill away from a chelator which is a monoamine, diamide, single thiol chelator. *See also, In re Baird*, 29 U.S.P.Q.2d 1550 (Fed.Cir. 1994).

Thus the rejection based on the Examiner's unwarranted expansion of the Harris formula to encompass the monoamine, diamide, single thiol metal chelator of the present claims should be overruled.

C. Neither reference provides motivation for the proposed combination.

As this Board has stated:

> [I]n order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*, preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. *(citations omitted, emphasis in original).*

Ex parte Levengood, 28 U.S.P.Q.2d 1300, 1301 (B.P.A.I. 1993). *See also, In re Deuel*, 34 U.S.P.Q.2d 1210, 1214 (Fed.Cir. 1995). The Examiner has identified no teaching, suggestion, incentive or inference in Harris or Fritzberg'514 to support the instant rejection.

For example, at pages 3-4 of the Office Action dated April 9, 1999, the Examiner states that

> [a]lthough the ligands may distribute in the kidneys, one of ordinary skill in the art would have been motivated to conjugate a targeting ligand to such chelators to gain the advantages of, 1) further increasing the organ (kidney) specificity or 2) target other organs or tissues with said ligands, as taught by, *inter alia*, Fritzberg.

Similarly, in the Advisory Action dated August 18, 1999, the Examiner states:

> . . .it is well known that such ligands may be conjugated with a targeting ligand to provide site specificity, as shown by Fritzberg.

Neither of these assertions fulfills the Examiner's evidentiary burden of stating a *prima facie* case of obviousness.

Harris and Fritzberg '514 would in fact not be combined by those of skill because the particular organs targeted by each reference are different. Harris is completely devoid of any teaching or suggestion of a target tissue other than kidney. Since Fritzberg '514 issued on February 25, 1992, well before the filing date of Harris (December 31, 1992), Harris had constructive knowledge of Fritzberg '514. A reasonable inference can thus be made that Harris chose **not** to direct those of skill to chelators linked to a targeting agent.

Moreover, while Fritzberg '514 generally discloses the desirability of localizing radionuclides at target organs, the only specific targets identified in the secondary reference are "lymph node pathology, deep venous thrombi and the detection and staging of neoplasms"[4], "tumors"[5], "cancer site"[6], "cancer cell-associated antigens"[7], and "tumor-associated antigen"[8]. Fritzberg '514 identifies copending application USSN 624,098 as

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[4] *See*, col. 1, line 65-col. 2, line 2.
[5] *See*, col. 2, line 4.
[6] *See*, col. 7, lines 10-11.
[7] *See*, col. 7, line 14.
[8] *See*, col. 7, line 22.

relevant literature disclosing technetium derivatives of MAG3 for evaluating renal function[9]. However, Fritzberg '514 did not specify kidney as a target organ. A reasonable inference can thus be made that Fritzberg '514 does not direct those of skill to use thiotriaza chelator/polypeptide conjugates to enhance biodistribution of radionuclides into the kidney.

In the absence of a specific suggestion to combine the references, no *prima facie* case of obviousness has been made as a matter of law. *See, In re Mayne*, 41 U.S.P.Q.2d 1451, 1454 (Fed.Cir. 1997). Accordingly, the rejection should be overruled.

D. The suggested combination is inoperative.

At col. 18, lines 12-16, Harris states:

> [l]ow background and rapid, efficient excretion are important features in renal imaging agents, allowing high quality images to be obtained with the minimal amount of radiopharmaceutical administered to the patient.

Appendix B includes copies of U.S.Pat.Nos. 5,380,513; 5,648,059; and 5,843,894, each of which is directed to methods for reducing renal uptake of antibody fragments. As stated at col. 2, line 68 to col. 3, line 19 of the '513 patent:

> One problem associated with the administration of immunoconjugates comprising antibody fragments such as Fab or Fv, is the tendency for the active moieties, e.g., radionuclides, to localize in the kidneys. Additionally, metabolites of immunoconjugates comprising whole antibodies or larger antibody fragments, such as $F(ab')_2$ fragments, may localize in the kidneys. In general, substances (such as active moieties) associated with a proteinaceous moiety and having a molecular weight of less than about 50,000 to 60,000 accumulate in the kidneys and are filtered as glomerular filtrate. Immunoconjugates comprising active moieties linked to Fab and Fv fragments in the kidneys are generally processed in the glomerular filtrate. Additionally, immunoconjugates comprising whole antibody and $F(ab')_2$ targeting moieties may be catabolized after in vivo administration to form Fab' or smaller proteinaceous fragments bound to active moieties, which may accumulate in the kidneys and be processed in the glomerular filtrate.

At col. 3, lines 25-28, the '513 patent states:

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[9] *See*, col. 1, lines 53-56.

> [l]ocalization, retention and reabsorption of active moieties of immunoconjugates and metabolites in the kidneys reduces the target:nontarget ratio of the immunoconjugate and has several undesirable effects.

At col. 3, lines 33-36, the '513 patent states:

> [f]urthermore, localization and reabsorption of the radioactive imaging agent in the kidneys may damage normal tissue, and it may mask target sites in proximity to the kidneys.

Similar statements appear at col. 2, line 63 to col. 3, line 30 of the '059 patent and at col. 1, lines 16-38 of the '894 patent.

The targeting agents identified in Fritzberg '514 include carbohydrates, glycoproteins, and polypeptides.[10]

> Of particular interest are immunoglobulin-like compounds or binding fragments thereof, e.g., Fab, $F(ab')_2$, and F_V fragments of antibodies. . .[11]

The only targeting agents specifically exemplified in Fritzberg '514 are antibodies and antibody fragments, which would be expected to accumulate and be retained in kidneys, as taught in the '513, '059, and '814 patents.

Thus the requirements of Harris, *i.e.*, rapid, efficient excretion and low background, could not be accomplished using the targeting moieties taught by Fritzberg, and in fact the Fritzberg targeting moieties would render the Harris chelators ineffective for their stated purpose. Accordingly, the rejection based on the combination of Harris and Fritzberg '514 should be overruled.

E. The combination of Harris and Fritzberg does not yield the present invention.

As Appellants have previously pointed out, even if the Harris general formula is substituted in such a way that it yields the Fritzberg formula, thus forming the basis of a proper combination, the result is not the presently claimed invention. If one X of the

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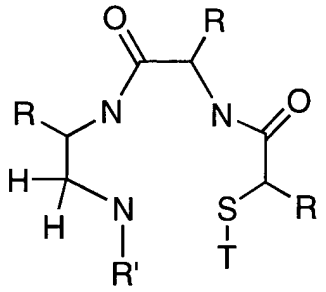
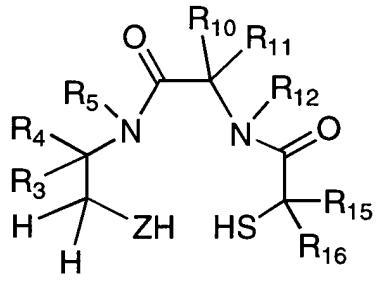
[10] Col. 6, lines 45-57.

Fritzberg formula is substituted as H_2 to form a monoamine, diamide, thiol chelator, Fritzberg's formula has the configuration set forth below.

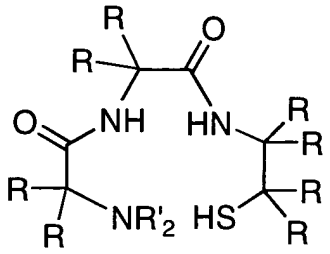


The formula of Harris is substituted as follows to yield the Fritzberg formula:

R_1 and R_2 must be H; n must be 0; R_6 and R_7 must form an oxygen atom; R_{13} and R_{14} must form an oxygen atom; and S must be exchanged with Z. The structure resulting from these substitutions is shown below.



In contrast, the chelator of claim 2 (shown with the n, m, and p variables each equal to 0 so that comparison with Fritzberg is facilitated) is set forth below.



[11] Col. 6, lines 57-60.

It is readily apparent that the structures of the cited references, when properly combined, do not teach or suggest the chelator of the present claims. *See, In re Mayne*, 41 U.S.P.Q.2d at 1455; *In re Jones*, 21 U.S.P.Q.2d 1941, 1944 (Fed.Cir.1992). Thus the suggested combination does not in fact yield the presently claimed invention, and the rejection of claims 2-8 and 10 over Harris in view of Fritzberg '514 should be overruled.

F. **The present facts do not justify hindsight reconstruction of the claimed invention from the cited references.**

Citing *In re McLaughlin*, 443 F.2d 1392, 170 U.S.P.Q. 209 (CCPA 1971), in the Office Action dated April 9, 1999 the Examiner opined that

> . . .so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

Current Federal Circuit precedent does not support the position that hindsight reconstruction of an invention is appropriate under any circumstances. Moreover, the instant rejection has clearly been constructed from the Appellants' disclosure, since the presently claimed formula is not taught or suggested in Harris or Fritzberg and cannot be obtained from the combination of these references. The rejection has been constructed as follows:

- Harris' express limitation to diaminethiol, diaminedithiol, or diamidodithiol chelators has been ignored;
- the Harris formula has been substituted to obtain the presently claimed formula;
- Fritzberg has been combined with the improperly substituted Harris formula.

The Federal Circuit has recently reiterated its caution against the hindsight trap in *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed.Cir. 1999).

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed.Cir. 1998) (describing "teaching or suggestion or motivation [to combine] as an "essential evidentiary component of an obviousness holding"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 U.S.P.Q.2d 1453, 1459 (Fed.Cir. 1998) ("the Board must identify specifically . . . the reasons one of

> ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed.Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed.Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 U.S.P.Q. 657, 667 (Fed.Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of the combination"); *See also Graham*, 383 U.S. at 18, 148 U.S.P.Q. at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight.

The Court has further elaborated on hindsight analysis:

> . . . an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *(citation omitted)*

In re Rouffet, 47 U.S.P.Q.2d at 1457.

Even if *In re McLaughlin* continues to be applicable law, the invention in *McLaughlin* was characterized by the Court as involving "only relatively simple mechanical concepts", 443 F.2d at 1395[12], in contrast to the present chemical invention. As stated in *In re Grabiak*, 226 U.S.P.Q. at 872: ". . . generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *See also, In re Jones*, 21 U.S.P.Q.2d 1941, 1943 (Fed.Cir. 1992). Regardless of the extent to which hindsight reconstruction in a simple mechanical case is appropriate, the law does not support use of a chemical application as a blueprint to reconstruct a chemical invention from isolated disclosures in the prior art.

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[12] Applicants question the continued viability of *McLaughlin* in light of the fact that the subject matter of the *In re Dembiczak* application was a Halloween-style pumpkin trash bag. 50 U.S.P.Q.2d at 1615.

IX. CONCLUSION

For all of the reasons set forth above, the rejection under § 103 of claims 2 through 8 and 10 over Harris in view of Fritzberg '514 is improper as a matter of law, and Appellants request that it be overruled.

Respectfully submitted,

DIATIDE, INC.

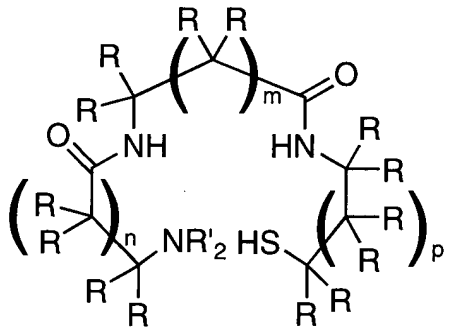
Patricia A. McDaniels

Patricia A. McDaniels
Reg.No. 33,194

9 Delta Drive
Londonderry, NH 03053
(603) 437-8970 (telephone)
(603) 437-8977 (facsimile)

Appendix A

2 (twice amended). A reagent comprising a targeting moiety covalently linked to a metal chelator having a formula:



wherein:

n, m and p are each independently 0 or 1,

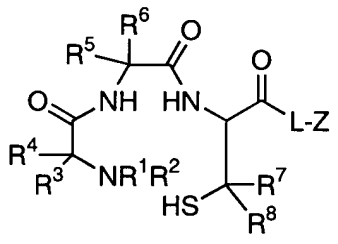
each R′ is independently H, lower alkyl, hydroxyalkyl (C_2-C_4), or alkoxyalkyl (C_2-C_4);

each R is independently H or R″, where R″ is substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group;

one R or R′ is L, wherein when an R′ is L, -NR'_2 is an amine; and

L is a bivalent linking group linking the chelator to the targeting moiety.

3 (amended). A reagent according to claim 2, wherein the metal chelator has a formula:



wherein:

R^1 and R^2 are each independently H, lower alkyl, hydroxyalkyl (C_2-C_4) or alkoxyalkyl (C_2-C_4);

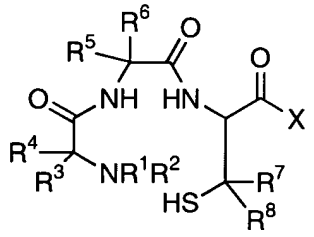
R^3, R^4, R^5, and R^6 are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group;

R^7 and R^8 are each independently H, lower alkyl, lower hydroxyalkyl or lower alkoxyalkyl;

L is a bivalent linking moiety; and

Z is a targeting moiety.

4 (amended). A reagent according to claim 2, wherein the metal chelator has a formula:



wherein:

R^1 and R^2 are each independently H, lower alkyl, hydroxyalkyl (C_2-C_4), or alkoxyalkyl (C_2-C_4);

R^3, R^4, R^5, and R^6 are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group, and one of R^3, R^4, R^5, and R^6 is Z-L-$(CR_2)_n$-, where n is an integer from 1 to 6 and each R is independently H, lower alkyl, or substituted lower alkyl;

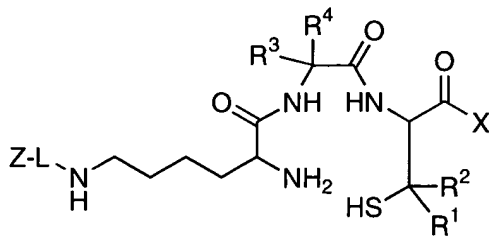
R^7 and R^8 are each independently H, lower alkyl, lower hydroxyalkyl or lower alkoxyalkyl;

L is a bivalent linking moiety;

Z is a targeting moiety; and

X is $-NH_2$, $-NR^1R^2$, or $-NR^1$-Y, where Y is an amino acid, an amino acid amide, or a peptide of from 2 to about 20 amino acids.

5 (amended). A reagent according to claim 4, wherein the metal chelator has a formula:



wherein:

R^1 and R^2 are each independently H, lower alkyl, hydroxyalkyl (C_2-C_4) or alkoxyalkyl (C_2-C_4);

R^3 and R^4 are independently H, substituted or unsubstituted lower alkyl or phenyl not comprising a thiol group;

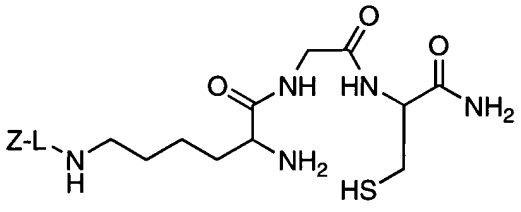
n is an integer from 1 to 6;

L is a bivalent linking moiety

Z is a targeting moiety; and

X is $-NH_2$, $-NR^1R^2$, or $-NR^1$-Y, where Y is an amino acid, an amino acid amide, or a peptide of from 2 to about 20 amino acids.

6. A reagent according to claim 5, wherein the metal chelator has a formula:



wherein:

L is a linker group; and

Z is a targeting moiety.

7 (amended). A reagent according to claim 2, wherein the metal chelator is selected from the group consisting of:

(amino acid)^1-(amino acid)^2-cysteine-,

(amino acid)^1-(amino acid)^2-isocysteine-,

(amino acid)^1-(amino acid)^2-homocysteine-,

(amino acid)^1-(amino acid)^2-penicillamine-,

(amino acid)^1-(amino acid)^2-2-mercaptoethylamine-,

(amino acid)^1-(amino acid)^2-2-mercaptopropylamine-,

(amino acid)^1-(amino acid)^2-2-mercapto-2-methylpropylamine-,

(amino acid)^1-(amino acid)^2-3-mercaptopropylamine-,

wherein:

(amino acid) is a primary α- or β-amino acid not comprising a thiol, and wherein the chelator is attached to a targeting moiety *via* a covalent bond with a carboxyl terminus of the chelator or *via* a side chain on one (amino acid).

8 (amended). A reagent according to claim 7, wherein (amino acid)^1 is either a α,ω- or β,ω-diamino acid having a free α-amine or β-amine.

10 (amended). A reagent according to claim 2, wherein the chelating group has a formula selected from the group consisting of:

Gly-Gly-Cys-
Arg-Gly-Cys-
-(ε-Lys)-Gly-Cys-
-(δ-Orn)-Gly-Cys-
-(γ-Dab)-Gly-Cys-
and
-(β-Dap)-Gly-Cys-.